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PSYCHONEUROENDOCRINE INTERVENTIONS AIMED AT ATTENUATING IMMUNOSENESCENCE – A REVIEW

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Abstract

There is evidence suggesting that immunosenescence can be accelerated by external factors such as chronic stress. Here we review potential psychoneuroendocrine determinants of premature aging of the immune system and discuss available interventions aimed at attenuating immunosenescence. Chronic stress may accelerate various features of immunosenescence by activating key allostatic systems, notably the hypothalamic-pituitary-adrenal axis. The immunological impact of such neuroendocrine dysregulation may be further amplified by a dramatic decline in dehydroepiandrosterone (DHEA) levels, acting in part as an endogenous glucocorticoid antagonist. Stress-buffering strategies show beneficial effects on various biomarkers in elderly populations. Likewise, supplementation of DHEA, melatonin or growth hormone has yielded significant beneficial effects in a number of studies, including: increased well-being, memory performance, bone mineral density and improved immunocompetence as evidenced by results of *in vitro* (T-cell proliferation, cytotoxicity, cytokine production), and *in vivo* immune challenges. However, the side-effects of hormonal supplementation are also discussed. Finally, moderate exercise via the promotion of cortisol/DHEA balance or epigenetic modifications, is associated with lower serum pro-inflammatory cytokines, greater lymphoproliferative responses and lower counts of senescent T cells. Taken together, these data suggest that immune system is plastic and immunosenescence can be attenuated psychoneuroendocrine interventions.

Introduction

Aging is associated with progressive changes in several key physiological systems including the immune system, which is continuously remodeled over the life course, a process known as immunosenescence. Many age-related diseases are directly associated with immunosenescence such as increased susceptibility to infectious diseases, neoplasias, metabolic diseases, osteoporosis and autoimmune diseases (Castle 2000). Most, if not all, age-related diseases have multifactorial etiology including intrinsic (e.g., genetic background) and extrinsic factors like health-related behaviors and chronic stress exposure (Bauer 2005).

The immunological changes observed during aging are found in similar magnitude following chronic stress or glucocorticoid exposure (reviewed in Bauer et al. 2009). Indeed, the thymic involution and related drop in naïve T-cell exports, increased memory and regulatory T cells, a Th1 to Th2 cytokine shift, reduced cell-mediated immunity (e.g. blunted T-cell proliferation), restricted TCRαβ repertoire in the CD4+ and CD8+ T cells, increased serum pro-inflammatory markers (inflammaging) and shorter telomere lengths are all similar found during aging, distress conditions and chronic glucocorticoid exposure (Ramirez et al. 1996; Wack et al. 1998; Elenkov and Chrousos 1999; Ashwell et al. 2000; Franceschi et al. 2000; Globerson and Effros 2000; Sapolsky et al. 2000a; Kiecolt-Glaser et al. 2003; Effros et al. 2005; Hoglund et al. 2006; Trzonkowski et al. 2006; Damjanovic et al. 2007; Sauce and Appay 2011). Considering these multitude of determinants, efforts have been made to characterize immunosenescence from a multidisciplinary perspective as well as to design broad interventions to attenuate the effects age-related immunological changes. This review will summarizes these approaches, by high-

lighting several key determinants of aging of the immune system as well as novel interventions aimed to mitigate its effects.

Stress factors as determinants of immunosenescence

Healthy aging has been associated with significant psychological burden (or distress). We have previously reported that strictly healthy elders (SENIEUR) were significantly more stressed, anxious and depressed than young adults (Luz et al. 2003; Collaziol et al. 2004). In accordance with increased psychological morbidity, the healthy elders had higher cortisol (45%) and lower dehydroepiandrosterone (DHEA, -54%) levels compared to young adults (Luz et al. 2003), indicating a neuroendocrine imbalance of the hypothalamic-pituitary-adrenal (HPA) axis. Increased cortisol levels were associated with a fall in the numbers of naïve T cells (Collaziol et al. 2004) and reduced T cell proliferation (Luz et al. 2006) during healthy aging. We argued that these neuroendocrine dysregulations may contribute to immunosenescence since all leukocytes exhibit receptors and are thus fully responsive for these neuroendocrine products.

However, healthy aging has been associated with reduced cellular responsiveness to glucocorticoids (GCs). The effects of GCs on the immune system are mediated via both intracellular and membrane GC receptors (GRs) (McEwen et al. 1997). Healthy elders had a reduced (–19%) *in vitro* lymphocyte sensitivity to dexamethasone (a synthetic GC) compared to young adults (Luz et al. 2003), suggesting acquired resistance to GCs. We hypothesize that high cortisol levels render lymphocytes resistant to steroids, thus promoting inflammation and "inflammaging". A recent study support this hypothesis, reporting that higher immune glucocorticoid resistance was associated with greater pro-inflammatory cytokine pro-

duction by cells of young adults infected with common cold virus (Cohen et al. 2012). Taken together, these data show correlations between healthy aging, increased psychological stress, activation of the HPA axis and specific immune changes characteristic of immunosenescence.

Chronic stress may lead to premature immunosenescence

Superimposing chronic stress during aging might thus accelerate features of immunosenescence. It is well known that chronic exposure to psychological stress is correlated with suppressive immune functions (Reviewed in Glaser and Kiecolt-Glaser 2005). These associations may be explained by accelerate aging of several lymphoid organs and key immunological functions (Bauer 2008). Stressed elders may thus be at risk for the development of stress-related pathologies because of detrimental additive effects of stress upon the aged immune system.

Is there any elderly population especially at risk for premature immunosenescence? Elderly caregivers of spouses with dementia represent such model to study the superimposing (and detrimental) effects of chronic psychological stress upon immunosenescence. Caregiving for the first-grade elderly relative with dementia is an exceptionally demanding task associated with increased stress, anxiety, depression and notably suppressed immune functions (Redinbaugh et al. 1995). A longitudinal study has shown that caregivers had increased mortality rate (>63%) compared to non-stressed controls (Schulz and Beach 1999). Caregiving for a chronically ill partner (stroke or dementia) is associated with increased susceptibility to upper respiratory infections, including influenza (Vedhara et al. 1999), and reduced immune responses to pneumococcal pneumonia vaccines

(Glaser et al. 2000). It has been shown that elderly caregivers of Alzheimer patients have impaired T cell proliferation (Bauer et al. 2000), reduced NK cell activity (Esterling et al. 1996), low salivary IgA levels (Gallagher et al. 2008), a reduced IL-2 production (Bauer et al. 2000) in contrast to higher TNF-α, IL-10 (Damjanovic et al. 2007) and IL-6 levels (Kiecolt-Glaser et al. 2003). Stress-related increase in proinflammatory cytokines, such as TNF-α and IL-6, have broad health-related implications, including: several age-related conditions like cardiovascular diseases, osteoporosis, arthritis, type II diabetes, some neoplasias, periodontal disease, frailty and functional decline (Harris et al. 1999). Chronic psychological stress has been correlated with increased oxidative stress, reduced telomerase activity and shorter telomere length, suggesting a state of premature cell senescence, which could implicated with reduced longevity (Epel et al. 2004).

What are the potential mechanisms involved with stress-related premature features of immunosenescence? There is evidence suggesting that neuroendocrine changes are responsible for such changes. Indeed, we have previously observed that elderly caregivers of dementia spouses had significantly higher cortisol levels compared to non-stressed elderly controls (Bauer et al. 2000). Acquired steroid resistance was also demonstrated at the cellular level: caregivers showed increased lymphocyte GC resistance compared to non-stressed elderly controls. Again, we hypothesize that high cortisol levels would render lymphocytes more resistant to steroids, further promoting “inflammaging”.

Taking together, chronic stress is involved in the premature dysregulation of key allostatic systems associated with accelerated immunosenescence. It should be considered that other lifestyle factors, coping strategies and tempera-

ment may also influence the pace of immunosenescence. It is expected that stress-management interventions would be beneficial for the elderly. The next section will review some interventions designed to reduce the impact of stress on immunosenescence.

Interventions aimed at attenuating immunosenescence

Psychosocial interventions

Psychosocial interventions have been effective in attenuating stress and promoting a better endocrine balance in the elderly. By reducing stress levels and promoting healthy behaviors, psychosocial interventions may also attenuate the rise in cortisol, decline in DHEA, and promote enhanced vagal tone, possibly resulting in better immune responses. For example, following a psychological enrichment program, elderly individuals showed increased levels of DHEA, testosterone, estradiol and growth hormone (GH) (Arnetz et al. 1983). This psychological enrichment program was designed to counteract social isolation and passivity by increasing social activation, competence, and independence. Another study showed that older adults who practiced relaxation techniques, had reduced antibody titers to latent Herpes Simplex virus-1 (HSV-1). Lower viral antibody titers suggest fewer episodes of viral-reactivation, indicating that a lifestyle intervention was associated with reduced chronic antigenic stimulation (Gouin et al. 2008). These studies suggest that stress-buffering strategies can lead to an improvement in cellular immunity involved in the control of latent viruses.

Resilience factors may also buffer the impact of stress on key allostatic systems (i.e. neuroendocrine and immune) of the elderly. Recent data produced by our laboratory have suggested that the maintenance of health during aging mini-

mizes the effects of chronic stress exposure (Jeckel et al. 2010). We recruited chronically stressed and non-stressed SENIEUR older adults and investigated neuroendocrine and immunological changes. The stressed group included caregivers of the first-grade elderly relative with dementia. Despite elderly caregivers of dementia patients were significantly more stressed than elderly controls without a caring burden, no changes in cortisol levels were observed. Positive neuroendocrine-immune interactions (eustress) were also observed in these strictly healthy and stressed elders. Healthy elderly caregivers exhibited increased T cell proliferation and higher cellular sensitivity to GCs compared to non-stressed healthy controls. Elderly individuals engaged in physically active behaviors do not experience enhanced levels of emotional distress (Wrosch et al. 2002) and have attenuated secretion of salivary cortisol (Wrosch et al. 2007). A strong resilience factor for health outcomes may be the induction and maintenance of positive emotion through personality and coping styles. Individuals reporting personality-type of positive affect have lower cortisol levels, reduced inflammatory markers (e.g. IL-6, CRP) and favorable associations with heart rate and blood pressure (Steptoe et al. 2009). In addition, stressed individuals with better social support had stronger immune responses to vaccination (Glaser et al. 1992). Therefore, resilience factors or stress-management interventions appear to be to modulate aspects of immunosenescence most likely by reducing endogenous GC levels.

DHEA supplementation

DHEA and its metabolites have been considered the natural endogenous antagonists of GCs (Hazeldine et al. 2010). Serum DHEA levels decrease significantly after the second decade of life in humans, and the elderly exhibit less than 5% of the concentrations seen in younger adults (Hornsby 1995). The im-

paired DHEA secretion, in parallel with increased cortisol levels, results in an enhanced exposure of leukocytes to deleterious effects of GCs (Butcher et al. 2005; Maninger et al. 2009; Khanfer et al. 2011). DHEA replacement therapy has yielded significant beneficial effects for healthy elders, including increased well-being, memory performance, bone mineral density and altered immune function (Buvat 2003; Nair et al. 2006; Kenny et al. 2010). DHEA replacement can increase glucose tolerance and reduce insulin resistance in elders (Weiss et al. 2011). In addition, flattened DHEA diurnal profile has been associated with impaired physical function during aging (Heaney et al. 2012). However, a recent systematic review indicated no conclusive evidence of benefits of DHEA replacement on muscle strength and physical function in clinical trials (Baker et al. 2011) – with no recommendation for this use in the elderly. DHEA replacement may also have protective cardiovascular properties, as it can improve arterial stiffness index in elders (Weiss et al. 2012). While the DHEA replacement can induce similar changes in both men and women, in some cases the effects can be genre-specifics, as DHEA replacement can improve the ovarian performance (Gleicher and Barad 2011).

Previous studies have investigated the immunomodulatory effects of DHEA *in vitro* as well as following *in vivo* supplementation (Suzuki et al. 1991). DHEA supplementation was associated with increased natural killer (NK) counts and cytotoxic function, as well as decreased IL-6 production and T-cell proliferation *in vitro*, and with increased secretion of IL-2 by T cells (Suzuki et al. 1991; Casson et al. 1993; Di Santo et al. 1996; Straub et al. 1998; Solerte et al. 1999; Hazeldine et al. 2010). Although both T and B cells can be stimulated *in vitro*, they require different DHEA concentrations (Sakakura et al. 2006). Because of its anti-

inflammatory properties, the potential benefits of DHEA have been investigated in autoimmune diseases. However, following encouraging studies demonstrating beneficial effects of DHEA supplementation in murine lupus models, the effect of DHEA on disease activity in lupus patients remains controversial (Sawalha and Kovats 2008). Previous studies have also explored the potential use of DHEA as adjuvant in vaccine preparations. Notwithstanding the clear adjuvant effects of DHEA during immunization to hepatitis B (Araneo et al. 1993) or influenza (Danenberg et al. 1995) in mice, negative effects have been reported following influenza vaccination in older humans (Danenberg et al. 1997; Degelau et al. 1997).

Overall, these data indicate the potential use of DHEA as anti-aging hormone and suggest that DHEA supplementation might attenuate chronic low-grade inflammation and age-related frailty by inhibiting production of pro-inflammatory cytokines. It should be kept in mind that very few data exist regarding the DHEA effects on the immune responses of the elderly and large clinical trials are thus necessary to disentangle conflicting reports. Some studies have found mild adverse effects in the study subjects, who had acne and hirsutism in general. A recent study reported that higher DHEA-S levels were associated with depressive symptoms, but not diagnosis of major depression, during menopausal transition (Morrison et al. 2011). Importantly, pharmacological DHEA levels have been associated with the development of hepatocellular carcinoma (Hazeldine et al. 2010).

Melatonin treatment

Melatonin supplementation could be of potential value for elders due its antagonistic effects on cortisol (Maestroni et al. 1986), as well as potentially

enhancing effects of cell-mediated immunity. The production of melatonin by the pineal gland begins as the eyes close and its secretion is associated with serotonin production, which is activated during the dark cycle. Furthermore, melatonin is also secreted by several leukocytes including monocytes, T and NK cells and mast cells (Hardeland et al. 2011). Similar to cortisol, melatonin secretion has a circadian rhythm. The peak secretion occurs at night and very low levels are observed upon waking in the morning. Importantly, melatonin is reduced in elderly individuals, together with a decrease in the amplitude of the circadian rhythm of this hormone (Bastien et al. 2003). Although the age-related reduction of the melatonin levels is considered as a predisposing factor for neurodegenerative diseases such as Alzheimer's, melatonin replacement therapy may have neuroprotective potential (Srinivasan et al. 2006; Cardinali et al. 2008; Markus et al. 2010).

The decline in melatonin levels during aging has been proposed to play an important role in immunosenescence (Cardinali et al. 2008). In addition to its sleep regulatory properties, melatonin is a natural antioxidant with important immunological properties. The immunomodulatory properties of melatonin are related in part to its actions on specific membrane (MT1 and MT2) or nuclear receptors located in leukocytes. The *in vitro* effects of melatonin include increased T cell proliferation (Konakchieva et al. 1995) enhancement of NK cell cytotoxicity (Currier et al. 2000) and increased production of several cytokines including IL-1, IL-2, IL-12, IL-6, TNF-α and IFN-γ (Garcia-Maurino et al. 1997; Garcia-Maurino et al. 1999; Chen and Wei 2002). Conversely, melatonin has anti-inflammatory properties including inhibition of NO synthases and 5-lipoxygenase (Hardeland et al. 2011). A recent *in vitro* study with human T-cell lines demonstrated that melatonin

efficiently downregulates the expression of retinoic acid-related orphan receptor alpha (RORα), a key transcription factor involved with differentiation of Th17 and regulatory T cells (Tregs) (Lardone et al. 2011). Melatonin also stimulates the production of glutathione, the most abundant antioxidant molecule found in mammalian cells. Aside from detoxifying hydrogen peroxide into water, glutathione is also essential for lymphocyte activation, proliferation and cytotoxicity (Suthanthiran et al. 1990; Liang et al. 1991). Thus, the immune-enhancing properties of melatonin may be in part due to maintenance of intracellular glutathione levels, and the subsequent effects on cell-mediated immunity (Cardinali et al. 2008). In support, melatonin administration increased the total number of thymocytes in old mice (Tian et al. 2003). This protective effect of melatonin on thymocytes was attributed to its anti-apoptotic action, by inhibiting GC-induced thymic apoptosis. Melatonin replacement has been effective in suppressing neoplastic growth in a variety of tumors, including breast and prostate cancer, melanoma, ovarian and colorectal cancer (Srinivasan et al. 2011). Melatonin showed beneficial effects in adjuvant therapy aimed to treat patients suffering from breast cancer, hepatocellular carcinoma or melanoma (Srinivasan et al. 2011). Although there are many studies showing the immunomodulatory properties of melatonin, there is a lack of investigations relevant to immunosenescence. However, the side-effects of melatonin replacement have been reported (e.g. daytime sleepiness, dizziness, headaches and interaction with others medications like anticoagulants and immunosupressants) and should be considered during long-term treatment.

GH and ghrelin replacement therapies

Aging significantly reduces pituitary GH levels, a phenomenon known as somatosenescence. The absence of appropriate GH-immune signaling may also

accelerate immunosenescence. GH-deficient mice exhibit immune dysfunction (including thymic involution), which can be reversed with GH replacement (Kelley 1990). Indeed, GH has many direct (or indirect effects via induction of IGF-1) immunoregulatory effects. For example, GH may enhance lymphocyte cytotoxicity (in both CD8+ T cells and NK cells), increase lymphocyte proliferation, promote the differentiation of neutrophils, as well as increase TNF-α and thymulin production (Welniak et al. 2002). The GH replacement in older subjects may not only modulate the levels of IGFs and IGFBPs but also with little gender-related differences (i.e. increase of IGF-1 and IGFBP -3 in both sexes; IGFBP-2 and IGFBP-5 increase only in men and immunoreactive insulin increase only in women) (Munzer et al. 2006). However, men may have a better response (IGF-1 levels) to GH replacement than women (Gotherstrom et al. 2007). The replacement can also increase the protein synthesis in elderly people, this effect is stronger in men when GH replacement is carried along with testosterone (Huang et al. 2005). In addition, GH is synthesized by leukocytes, mimics the action of IFN-γ, increasing the activity of phagocytes (Kelley 1990). GH replacement therapy may be of clinical value by restoring immune competence in the elderly. However side effects of GH therapy also exist. For instance, GH administration could reduce the levels of sex hormones, promoting secondary changes in the immune system, obesity and even cancer (Lo et al. 2001).

Considering patients with GH deficiency, the replacement has shown beneficial effects to the thymus and to the T-cell proliferation as well as bone mineral density, which reinforces the concept that GH is capable to attenuate senescence (Morrhaye et al. 2009; Elbornsson et al. 2012). Furthermore, we have

previously observed that low pituitary GH levels were not associated with a reciprocal decline in immunoreactive GH produced by lymphocytes during human aging (Luz et al. 2006). The potential side-effects of long-term GH replacement shall be considered, and include carpal tunnel syndrome, arthralgia, increased risk for diabetes (as it increases insulin resistance) and it has been associated with increased risk for Hodkin's lymphoma (Freedman et al. 2005).

Reduced ghrelin levels during aging may also contribute to immunosenescence. Ghrelin binds to a GH secretagogue receptor (GHS-R) expressed on lymphoid cells, having anti-inflammatory effects (lowering TNF-α, IL-1 and IL-6 levels) (Dixit et al. 2004). Ghrelin is produced by stomach cell, which modulates energy balance, stimulating appetite and pituitary GH secretion. Ghrelin may be an important factor for thymopoiesis during aging as mice deficient for ghrelin or GHS-R showed profound age-related thymic involution. In contrast, ghrelin replacement in old mice is associated with increased thymic mass, and a greater production of recent thymic emigrants with enhanced TCR diversity (Dixit et al. 2007). The ghrelin replacement can increase the GH secretion in elders (Nass et al. 2008), and can also help to increase the bone mineral density in women (Napoli et al. 2011). Cytokine replacement could be also of interest in rejuvenating thymopoiesis and T-cell function. Sportés et al. have recently shown that IL-7 can rejuvenate the aging immune system in humans by promoting thymopoiesis (increasing the numbers of naïve T cells) and expanding TCR repertoire diversity (Sportes et al. 2008). In addition, it was shown that treatment with thymosin α1 (Tα1) resulted in increased T-cell responses (e.g., cytokine production, proliferation and cytotoxicity). Tα1 is a 28-amino acid biologically active protein that has pharmacologic effects enhancing

cellular immunity. Tα1 administration was highly effective in the restoration of cell-mediated functions when used in combination with cytokines (Naylor et al. 2007). However, the long-term beneficial effects of ghrelin replacement therapies should be considered with caution as it can be pro-oncogenic (Akamizu and Kangawa 2012).

Regular moderate-intensity physical activity is associated with better immune responses

Physical activity is associated with many beneficial health effects, and has the advantage of being a non-invasive, low-cost and easy to implement therapy or intervention. Interventions including health behavior changes are likely to be more effective in attenuating aging of the immune system. Indeed, increasing fitness is probably one of the most powerful interventions in restoring cortisol/DHEA balance and can improve psychological and physiological well-being. Long-term moderate-intensity exercise can decrease cortisol and increase DHEA, GH and IGF-1 levels (Cotman and Berchtold 2002), as well as reduced anxiety (Petruzzello et al. 1991) and depression (Barbour et al. 2007).

Moderate-intensity exercise has been associated with anti-inflammatory effects, including lowering serum TNF-α, IL-6 levels and higher IL-10 and Treg counts (Gleeson et al. 2011). These effects might be mediated by the reduction of visceral fat mass and correlated decreased released of adipokines, as well as the induction of the anti-inflammatory environment promoted by the moderate-intensity exercise. In addition, moderate-intensity exercise training in the elderly can also increase T-cell proliferation, reduced the frequency of senescent T-cells (i.e. CD45RO+, KLRG1+, CD57+, CD28-), enhance IL-2 production and T-cell expression of the IL-2 receptor, and is associated with longer leukocyte telomeres

and better *in vivo* immune responses to vaccines and recall antigens (Simpson and Guy 2010). Ogawa and col. compared the Th1/Th2 cytokines in active vs. sedentary elderly, and observed greater numbers of IL-2 secreting CD8+ cells in physically active elderly compared to those who were sedentary (Ogawa et al. 2003). Enhanced T-cell responses may be associated with stronger immunity to control viral and bacterial infections: It has been reported that physically active elderly women have a lower risk of community-acquired pneumonia compared to sedentary elderly women (Baik et al. 2000). On the other hand, a lack of regular exercise is associated with an increased the risk of hospitalization due to infection (Leveille et al. 2000). This concept concurs with another study suggesting that physical activity may increase mucosal immune responses in the elderly, promoting resistance to upper respiratory infections (Sakamoto et al. 2009).

Moderate-intensity exercise also appears to buffer the age-related increase in pro-inflammatory cytokines via epigenetic modifications. For instance, the methylation of the pro-inflammatory ASC gene, involved in the secretion of IL-1 and IL-18, reduced significantly with age, suggesting an age-related increase in ASC expression (McGee et al. 2009). Of particular note, the ASC methylation levels were higher in the older exercise group than in the older controls. To what extent these changes are related to cortisol/DHEA balance induced by moderate-intensity exercise is largely unknown.

Conclusions and future perspectives

Normal aging is associated with major changes in key allostatic systems, notably immune and neuroendocrine, that increase the risk for age-related diseases. These effects do not appear driven by reverse causality (i.e., an effect of

age-related health impairments on immunity), as healthy aging is also associated with significant psychological distress and HPA axis activation (increased cortisol and reduced DHEA levels). Although the exact mechanisms of immunosenescence remain to be elucidated, it is becoming apparent that many of the physiological changes associated with aging are characterized by epigenetic modifications (Fraga and Esteller 2007).

We reviewed here that psychological or pharmacological strategies aimed to attenuate or prevent the increase in HPA axis activation with aging may benefit the elderly. Many studies aimed to understand how lifestyle factors promote or maintain good health. In this scenario, for instance, regular moderate-intensity physical activity may help to delay the onset of immunosenescence. Some clinical strategies, such as hormone replacement or cytokine therapy may be useful to attenuate immunosenescence. However, the potential harmful side-effects of prolonged hormonal supplementation shall be also considered.

The concept of hormesis should be discussed here considering the genetic, hormonal and lifestyle factors involved in accelerating or buffering immunosenescence. Aging, senescence and death are the final consequences of impaired homeostasis or failure of homeodynamics (Rattan 2006). The most important component of homeodynamics is represented by the capacity of living systems to deal (cope) with stress. A progressive shrinking of the homeodynamic space (or buffering capacity) is the hallmark of aging and strongly associated with age-related diseases (Rattan 2008). The stress responses in mammals include apoptosis, inflammation, and increased glucocorticoids – that are also associated with healthy aging. The clinical consequences of stress responses can be both

harmful and beneficial, depending on characteristics of the stressor (Calabrese 2008). This phenomenon of biphasic dose response was termed hormesis (Southam and Ehrlich 1943) and it has been described across different disciplines including toxicology, pharmacology, medicine, radiation biology and gerontology (Calabrese et al. 2012). A good example of stress-induced hormesis is the beneficial effects of moderate exercise (hormetic agent) to increase immunity and lower levels of oxidative stress (Radak et al. 2008). Physical inactivity or overtraining are associated with damaging oxidative stress and blunted immune responses. Furthermore, acute or mild stress is generally associated with enhanced immune functions (Dhabhar and McEwen 1999), which prepare the organism to better cope with the stressor. In contrast, chronic stress, which is not resolved via coping or adaptation, is considered to be *distress* and it has been associated with suppressed immune functions (Glaser and Kiecolt-Glaser 2005) and inflammation (Kiecolt-Glaser et al. 2003). These effects are related to GC concentration and to duration of tissue exposure to peripheral GCs. For instance, low cortisol levels produce permissive or stimulatory immune changes whereas long-term or high cortisol levels are immunosuppressive (Sapolsky et al. 2000b). Hormetic stressors (hormetins) can be applied successfully to interventions in aging and can be categorized as physical, nutritional, or psychological hormentins (Rattan 2008). Moderate exercise, hormonal and nutritional supplementation, and psychosocial interventions are good examples of stress-induced hormesis aimed to improve homeodynamic space in aging. Recent studies suggest that lifestyle factors (such as physical activity) and human health may be linked through epigenetic mechanisms such as DNA methylation, histone modifications and micro-RNAs (Sanchis-Gomar et al. 2012).

Therefore, by favoring hormesis, the interventions reviewed here would render epigenetic changes involved with the attenuation of immunosenescence.

In comparison to younger adults, the elderly who are chronically stressed may be at a greater risk of stress-related pathologies. Therefore, stress management and psychosocial support should promote a better quality of life for the elderly as well as reducing hospitalization costs. Preliminary evidence suggests that differences in personality traits (temperament) and coping skills could have protective properties. Finally, the maintenance of regular moderate-intensity physical activity, social support, personality (positive affect) and coping skills may protect the elderly from the detrimental effects of chronic stress exposure. More studies are needed to address the relationships of health-related behaviors on immunity that might promote better resilience to stress exposure.

This review has presented current evidence that it is possible to attenuate and potentially reverse many features of immunosenescence via stress-management therapies, improved health-related behaviors, and hormone replacement therapies. Low-cost practices, such as moderate regular exercise, may also allow us to age healthily by attenuating the effects of immunosenescence.

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Figure Legend

Figure 1. Some interventions aimed at attenuating immunosenescence. Hormonal replacement therapies have been effective to reduce inflammaging and improve several thymic-related functions such as higher cellularity and T-cell proliferation, cytokine production, and T-cell repertoire (TCR) diversity. However, the side-effects of long-term hormonal therapies should be considered. Stress-management and regular physical exercise have also been shown to reduce inflammaging and improve T-cell functions most likely via increasing DHEA and reducing cortisol levels as well as via epigenetic modifications.